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A novel ring-opening based tandem domino process of an activated vinyl cyclopropane

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Abstract

An activated vinyl cyclopropane reacted with substituted benzaldehydes to afford α-methylene γ-butyrolactones in the presence of DABCO·6H_2O. This tandem domino process took place in aqueous media, and was presumably initiated with the ring opening of cyclopropane by the nucleophilic addition of DABCO·6H_2O.

Tandem reactions have attracted particular attention over the past few decades because of their high efficiency in construction of complex molecular framework.[1] As versatile 3-carbon building blocks in modern organic syntheses, activated cyclopropane derivatives have been widely investigated in the field of nucleophilic ring-opening reactions.[2] Ring opening of activated cyclopropanes by nucleophiles gives carbanion (usually an enolate by the so-called homologous Michael addition), which can be subsequently trapped by electrophiles to form new carbon–carbon bonds through a tandem domino process.[3] This strategy is extremely efficient to construct the carbon framework of organic molecules. As a 5-carbon synthon, vinyl cyclopropanes (VCPs) usually activated by not less than one electron-withdrawing group (EWG), can also undergo nucleophilic ring opening with either 1,3- or 1,5-mode (Fig. 1). The 1,5-mode ring opening by nucleophilic addition,[4] usually promoted by metal, can provide potential utilities in organic synthesis. However, to the best of our knowledge, there are very limited reports taking advantage of the aforementioned tandem strategy on activated VCPs.[5] Herein, we report a novel metal-free tandem domino process based on the 1,5-mode nucleophilic ring opening of VCP affording the compounds with an α-methylene γ-butyrolactone core structure.

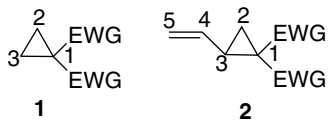

Fig. 1. Modes of ring opening of activated cyclopropanes and VCPs.

To further explore the chemistry of activated VCPs and make use of them as 5-carbon synthons to construct complex molecules by the tandem nucleophilic ring-opening reactions, we synthesized a functionalized VCP (**3**).[6] We conceived that nucleophiles may attack **3** at C-1 position, and the cleavage of 3-member ring would lead to an allylic carbanion, which could subsequently be trapped by various electrophiles (Scheme 1). Because of both the steric and the electronic effects, the intermediate with anion at C-5 position would be more stable than that with anion at C-3 position and therefore preferred to undergo 1,5-mode coupling rather than 1,3-mode coupling. We envisioned that tertiary amines, such as DABCO·6H_2O, may promote the ring opening of **3**.[7] The preliminary results showed a 1,5-mode, however, to our surprise, some more complex transformations happened in aqueous media to afford a 5-member ring lactone with moderate to good stereoselectivity.

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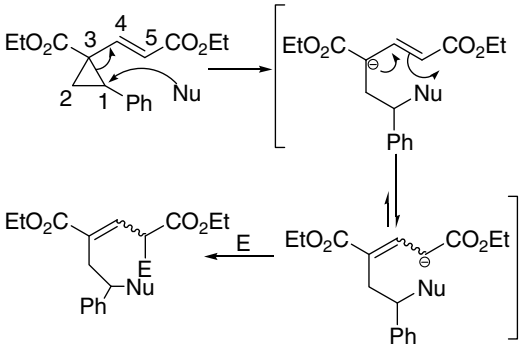
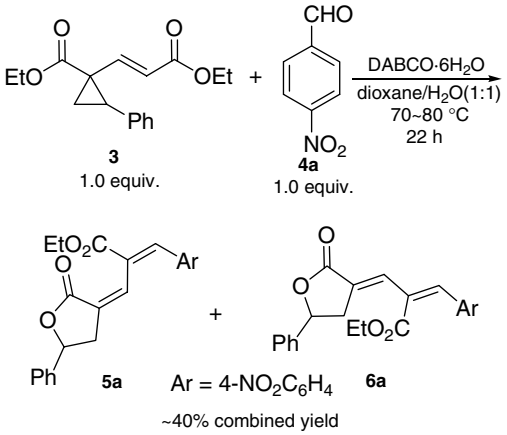


Scheme 1. Designed nucleophilic addition-initiated tandem domino process of **3**.



Scheme 2. DABCO·6H_2O-mediating tandem domino ring-opening reaction of **3** and **4a**.

In our initial attempts, no reaction of **3** with 4-nitrobenzaldehyde and anhydrous DABCO occurred in a variety of organic solvents, even with prolonged reaction time or at elevated reaction temperature. Surprisingly, when we chose 1,4-dioxane and water (v/v = 1:1) as a binary solvent system, two unexpected isomeric products (**5a** and **6a**, with a ratio of 3.8:1) were obtained.[8] The combined yield of **5a** and **6a** was 40%, together with 26% of recovered **4a** (Scheme 2).

To drive the reaction to completion, a large excess of **4a** (up to 10.0 equiv) was employed, but resulting in no improvement of the yield. The best ratio of **3** to **4a** was 1.2:1.0 with a yield of 48% (based on **4a**), still with 32% of recovered **4a**. Other Lewis bases (DBU, DMAP, Et_3N, $N(CH_2CH_2OH)_3$ and PPh_3) were also tested but gave no positive results. Use of a stoichiometric amount of DABCO·6H_2O (1.0 equiv to **3**) was necessary. With a catalytic amount of DABCO·6H_2O, the reaction was very slow and the yield was lower.

The solvent effect was also examined for the reaction of **3** with **4a** in the presence of DABCO·6H_2O.[9] CH_3CN/H_2O system was the best choice. It increased the reaction rate and afforded moderate yield (50% based on **4a**). The ratio of the organic solvent to water was important under these conditions. The mixed solvents with 1:1 (v/v) ratio were optimized for both the reaction rate and the yield. The ratio of the organic solvent to water did not significantly affect the stereoselectivity (the ratio of the two isomers). Some water-tolerant additives such as $Yb(OTf)_3$ and $Cu(OTf)_2$ were also employed. Instead of activating the carbonyl of **4a**, these two Lewis acids accelerated the decomposition of **3**.

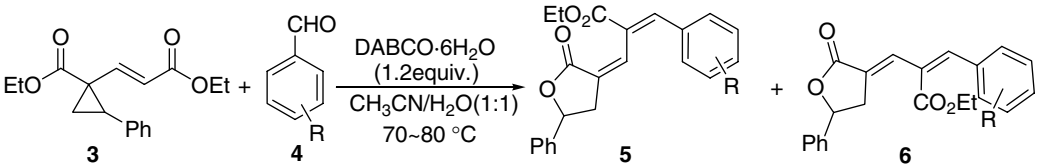
Under the optimized reaction conditions, we next carried out the reactions of **3** with a number of substituted benzaldehydes (Table 1). In most cases, when excess amount of **3** was used, the conversions were over 90%, while a moderate to large amount of substituted benzaldehydes were recovered. Substituents on the benzene ring greatly affected the reaction rates, yields and stereoselectivities. Strong electron-withdrawing groups (Table 1, entries 1–5), which could increase the electrophilicity of carbonyl, accelerated the reactions with relatively higher yields; while the aldehydes bearing the electron-donating groups (Table 1, entries 13 and 14) gave no desired products. These results indicated that carbanion intermediates were generated by the nucleophilic addition of DABCO·6H_2O. Most products were obtained with good stereoselectivities (Table 1, entries 2–5 and 7–11). Relative stereochemistries were determined by X-ray crystallography of **6a** and **5h**,[10] as well as analysis of NOESY and chemical shifts of two olefinic protons. When ethyl glyoxylic acetate and cyclohexanecarboxaldehyde were employed in the reactions, no desired products were observed.

A plausible mechanism for the DABCO·6H_2O-mediated tandem domino reactions of **3** was proposed as shown in Scheme 3. DABCO·6H_2O could attack **3** either at C-4 (path **a**) or C-1 (path **b**)[7] position to initiate the cascade process. In path **a**, Baylis–Hillman intermediate **7** could be generated. Intermediate **9** could be afforded by the addition of another molecule of DABCO·6H_2O followed by elimination. In path **b**, the ring cleavage of cyclopropane could lead to the formation of allylic carbanion intermediate **8,** which should isomerize to the electronically and sterically more stable intermediate **9**. Intermediate **9** could react with the electrophilic aldehydes to afford **10**. After dehydration, **12** could be obtained. Carbonyl at C-3 position could attack C-1 to form oxonium **13**, which should undergo the subsequent transformations to afford the final products.[11] The substitutent effects observed (Table 1) were consistent with the proposed mechanism.

In conclusion, we have developed a novel tandem domino process involving the nucleophilic ring-opening of VCP (**3**) by DABCO·6H_2O, the subsequent coupling reactions with substituted benzaldehydes **4** and lactonizations. Although the reactions proceed in low to moderate yields, and are limited to certain substituted aldehydes, this work provides a potential synthetic strategy to use the VCP as a 5-carbon synthon through a 1,5-mode

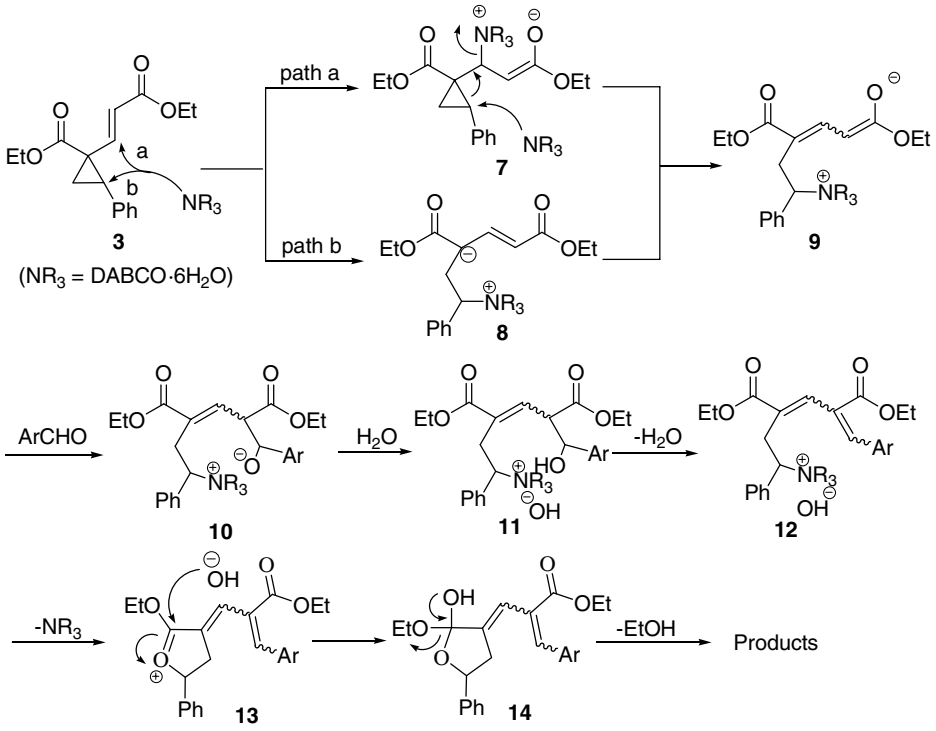
nucleophilic addition ring opening by a non-metal promoter. Further studies on the scope of the reactions and the synthetic applications are now being carried out in this laboratory.

Table 1
DABCO·6H_2O meditated ring-opening reactions of **3** and substituted benzenaldehydes **4**



Entry	Substrate	R	Conv. of **3** (%)	Conv. of **4** (%)	Time (h)	Product	Yield[a] (%)	Ratio[g] (**5**:**6**)
1	**4a**	4-NO_2	>90	67	18	**5a**, **6a**	50[b]	2.5:1
2	**4b**	3-NO_2	>90	65	22	**5b**, **6b**	51[b]	>20:1
3	**4c**	2-NO_2	>90	66	23	**5c**, **6c**	53[b]	>20:1
4	**4d**	4-CN	>90	63	53	**5d**, **6d**	42[b]	>20:1
5	**4e**	3-CN	>90	65	64	**5e**, **6e**	41[b]	>20:1
6[f]	**4f**	2-CN	<10	100	1	**5f**, **6f**	0	
7	**4g**	3-CF_3	77	42	63	**5g**,**6g**	31[b]	>20:1
8[d]	**4h**	3,5-2CF_3	74	>90	56	**5h**, **6h**	28[c]	>20:1
9[e]	**4i**	2,4-2CF_3	73	>90	44	**5i**, **6i**	29[c]	>20:1
10	**4j**	4-Cl	>90	23	72	**5j**, **5j**	20[b]	>20:1
11	**4k**	4-I	>90	26	48	**5k**, **6k**	23[b]	>20:1
12	**4l**	H	>90	>90	30		Trace	
13	**4m**	OH	<10	<10	28		0	
14	**4n**	OCH_3	>90	<10	46		0	

[a] Combined yield of **5** and **6**.
[b] Isolated yields based on **4**.
[c] Isolated yields based on **3**.
[d] With 1.0 equiv of **3**, 1.2 equiv of **4** and 1.0 equiv of DABCO·6H_2O.
[e] With 1.0 equiv of **3**, 3.0 equiv of **4** and 1.0 equiv of DABCO·6H_2O.
[f] **4f** reacted with DABCO·6H_2O to give unknown products in 1 h.
[g] Determined by chemical shifts of two different olefinic protons according to ^{1}H NMR.



Scheme 3. Proposed mechanism of the tandem domino reactions of **3** and aldehydes mediated by DABCO·6H_2O.

Acknowledgements

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8. *Physical data for compound* **5a**: ^{1}H NMR: δ 1.32 (t, $J = 7.2$ Hz, 3H); 3.04–3.12 (m, 1H); 3.54–3.60 (m, 1H); 4.31 (q, $J = 7.2$ Hz, 2H); 5.61 (t, 1H); 6.67 (s, 1H); 7.32–7.40 (m, 5H); 7.53 (d, 2H); 7.71 (s, 1H); 8.19 (t, 2H). ^{13}C NMR: δ 14.16, 37.65, 61.69, 78.22, 123.63, 125.39, 128.68, 128.85, 129.64, 130.48, 131.42, 137.96, 139.50, 141.13, 147.65, 165.74, 168.38. HRMS (ProMALDI) calcd for $C_{22}H_{19}NO_6Na$ $(M+Na)^+$: 416.1105, found 416.1100. IR (film): ν 3067, 3035, 2963, 2853, 1755, 1714, 1593, 1520, 1344, 1261, 1094, 1021, 800, 700 cm^{-1}. *Physical data for compound* **6a**: ^{1}H NMR: δ 1.34 (t, $J = 7.2$ Hz, 3 H); 2.42–2.48 (m, 1 H); 3.02–3.08 (m, 1H); 4.32 (q, $J = 7.2$ Hz, 2H); 5.47 (t, 1H); 7.17–7.33 (m, 5H); 7.44 (s, 1H); 7.54 (d, 2H); 7.80 (s, 1H); 8.18 (d, 2H). ^{13}C NMR: δ 14.19, 35.93, 62.03, 78.05, 123.96, 125.15, 128.62, 128.78, 129.63, 130.41, 130.67, 130.83, 139.58, 140.56, 147.93, 165.16, 170.22. HRMS (MALDI) calcd for $C_{22}H_{19}NO_6Na$ $(M+Na)^+$: 416.1105, found 416.1105. IR (KBr): ν 3061, 3039, 2986, 2964, 2900, 2854, 1753, 1713, 1669, 1625, 1598, 1523, 1346, 1255, 1203, 1023, 855 cm^{-1}.
9. Various solvents such as DME, DMF, THF, EtOH, dioxane and CH_3CN were employed. Yields were low to moderate and the recovery of **4a** was always observed. Stereoselectivity of the product was not significantly affected by solvents.
10. The crystallographic data (excluding structure factors) of **6a** and **5h** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 655766 and 655765, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. When **3** and **4a** reacted in the same solvent system at room temperature for one week, both of the two reactants were consumed and there was a fluorescent compound detected by TLC. After being heated for 6–8 h, the fluorescent compound disappeared and the final products were produced. This fluorescent compound was a high polar solid and had a good solubility in water. A try to separate and characterize this compound failed due to its unstability. We assumed this as an intermediate—a tertiary ammonium salt (or base) formed after the ring opening of cyclopropane by DABCO·6H_2O.